REMARKS

In response to a previous restriction requirement, claims 1-4 and 15-18 were elected. Claims 5-8 and 14 have been cancelled, with the right to pursue them in a continuation application being preserved. By this amendment, claim 1 has been amended. Accordingly, claims 1-4 and 15-18 are pending in the application.

Applicants would like to thank Examiner Counts for pointing out that a certified copy of the priority document has not been received. Filed herewith is a certified copy of the priority document, EP 01201107.8.

In the office action mailed February 28, 2002, the Examiner has rejected claims 1-4 and 15-18 under 35 U.S.C. §§112 and 103. In response thereto, Applicants provide the following:

The Invention

Applicants' invention is based on their discovery of a novel, insulin assay with a short turnaround time. The invention is for a real time test system that has at least one reservoir and at least one photomultiplier detector. The reservoir comprises monoclonal anti-insulin or anti-C peptide capture antibodies solidified in the reservoir. The reservoir is capable of receiving a sample, a wash solution, and labeled monoclonal anti-insulin or anti-C peptide antibodies. The labeled antibodies allow photometrical detection.

The invention allows a clinician to carry out an insulin assay at the location where the immediate test results are needed. The invention is especially useful in intra-operative applications, such as, for example, during surgery for multiple insulinomas (pancreatic tumors). Intraoperatively, the invention will assist the surgeon in locating the affected areas of the pancreas with accuracy. The invention can be used for *in vivo* and *ex vivo* applications.

Rejections under 35 U.S.C. §112

Claim 1 has been rejected under §112, second paragraph, as being indefinite with respect to the term "solidified" and the phrase "capable of."

Claim 1 recites "anti-insulin or anti-C peptide antibodies are solidified in said reservoir." The Examiner contends that the term "solidified" is vague and that it is unclear what the Applicant intends.

The term "solidified" has basis in the specification on page 5, line 17 and page 6, lines 17-20, and is defined by its ordinary meaning. For example, according to the Merriam-Webster Online Dictionary (See www.m-w.com), solidified is defined as "possessing or characterized by the properties of a solid, neither gaseous or liquid." Applicants are unaware of any alternate definitions of the term "solidified."

Applicants submit that one of ordinary skill in the pertinent art would interpret claim 1 to cover antibodies that have the properties of a solid, i.e. solidified. Thus, the term "solidified" in claim 1 sets forth the subject matter of the invention with a reasonable degree of clarity and particularity.

Accordingly, Applicants respectfully request that the Examiner reconsider the rejection under §112 of the term "solidified."

Claim 1 contains the phrase "capable of" with respect to the reservoir's ability to receive a sample, a wash solution, and labeled monoclonal anti-insulin or anti-C peptide antibodies. The Examiner has rejected the phrase "capable of" as being vague and indefinite and has posed the questions "Can the reservoir receive a sample ...or not."

By this amendment, claim 1 has been amended for clarification and now reads "...wherein said reservoir is capable of receiving a wash solution,..."

Applicants submit that amended claim 1 clearly states that the reservoir is capable of receiving a sample, etc. Accordingly, Applicants respectfully request that the rejection under §112 of the phrase "capable of" be reconsidered and withdrawn.

Rejections under 35 U.S.C. §103

Claims 1, 3, and 4 have been rejected under §103(a) as being unpatentable over U.S. Patent No. 6,232,113 to Coassin, in view of U.S. Patent No. 6,103,537 to Ullman and U.S. Patent No. 5,939,269 to Goldfine.

Coassin et al. disclose multi-well plates for fluorescent measurements of biological and biochemical samples. The multi-well plates of Coassin et al. comprise a layer of a particular cycloolefin polymer having low fluorescence and a high degree of transmission.

As discussed above, the claimed invention is for a real-time test system that requires at least one reservoir and at least one photomultiplier detector. The reservoir must comprise monoclonal anti-insulin or anti-C peptide capture antibodies solidified in the reservoir. The reservoir must be capable of receiving a sample, a wash solution and labeled monoclonal anti-insulin or anti-C peptide capture antibodies. The labeled antibodies must allow for photometrical detection.

In the office action, the Examiner admits that Coassin et al. do not disclose the use of monoclonal anti-insulin antibodies, labeled monoclonal anti-insulin antibodies or a wash solution in the reservoir.

More important, Coassin et al. do not disclose or suggest a system that has both at least one reservoir and at least one photomultiplier, nor do they disclose using their multi-well plates to photometrically detect labeled antibodies.

In the office action, the Examiner points to col. 21, lines 1-5, in support of the contention that Coassin et al. disclose the use of a photomultiplier detector. Applicants respectfully disagree with this contention.

In col. 21, lines 1-5, Coassin et al. describe an experiment they conducted in order to test the fluorescence properties of cycloolefins as compared to other polymeric materials used in multi-well plates. It is true that Coassin et al. utilized the photomultiplier tube of a Fluorimeter as part of their test. However, there is absolutely no suggestion to use photomultiplier detection for labeled antibodies. Moreover, there is not suggestion of a system that has at least one reservoir and at least one photomultiplier.

The Examiner cites Ullman et al. as disclosing the use of both anti-insulin monoclonal antibodies and labeled monoclonal insulin antibodies, as well as photomultiplier detection. Based on the combined teachings of Coassin et al. and Ullman et al., the Examiner contends that it would have been obvious to one of ordinary skill in the art to incorporate the use of labeled anti-insulin and insulin antibodies into the device of Coassin et al. Again, Applicants respectfully disagree.

But for the fact that Ullman et al. utilize anti-insulin antibodies in Example 35 (col. 35), the methods disclosed in Ullman et al. are wholly unrelated to the claimed invention. Ullman et al. disclose capillary assays for separating free and bound particles. The method of Ullman et al. comprises binding a member of a specific binding pair to a synthetic particle which uniformly migrates during capillary electroseparation.

There is simply no motivation in the prior art to utilize the electroseparation techniques of Ullman et al. in conjunction with Coassin et al.'s cycloolefin coated multi-well plates. Even if one were to incorporate the use of anti-insulin antibodies in the device of Coassin et al., they would not arrive at the test system of the claimed invention.

Goldfine et al. is cited as disclosing the use of a wash solution received in a 96 well plate which contains anti-insulin receptor monoclonal antibodies. Applicants appreciate the relevance of Goldfine et al. because Goldfine et al. are concerned with a related technical field, namely, insulin resistance.

However, the methods disclosed in Goldfine et al. differ considerably from the claimed invention. Goldfine et al. use antagonists for an insulin receptor tyrosine kinase inhibitor protein. According to Goldfine et al., a sample is contacted with a first anti-inhibitor antibody under conditions allowing immunospecific binding. Subsequently, the amount of the inhibitor in the sample is detected using the well known ELISA technique.

Goldfine et al. do not disclose monoclonal anti-insulin or anti-C peptide catching antibodies as in the claimed invention, or photometrical detection of labeled antibodies.

Upon combining the above references, one of ordinary skill in the art would not arrive at or near the claimed invention. In addition to the distinctions discussed above, none of the cited references disclose a reservoir having solidified anti-monoclonal anti-insulin or anti-C peptide catching antibodies.

The Examiner has not provided evidence of, and Applicants are unable to find, any suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the teachings of the cited references and arrive at the claimed invention.

In order to establish a *prima facie* case of obviousness, one of the criteria to be met is that the prior art references, when combined, must teach or suggest all of the claim limitations. See MPEP §2142.

As already discussed, Applicants` have demonstrated the important aspects of the claimed invention, which include:

i. at least on reservoir and at least one photomultiplier;

ii.. the reservoir must have having solidified monoclonal anti-insulin or anti-C peptide antibodies;

iii. the reservoir must being capable of receiving a sample, a wash solution and labeled monoclonal anti-insulin or anti-C peptide antibodies;

iv. the labeled antibodies must be photometrically detectable.

Upon combining the teachings Coassin et al. with Ullman et al. and Goldfine et al., all of Applicants' claimed limitations are not taught or suggested. Therefore, based on the foregoing discussion, Applicants' claimed invention is not obvious over Coassin et al. in view of Ullman et al. and Goldfine et al.

Accordingly, Applicants respectfully request that the rejection under §103 (a) based on Coassin et al. in view of Ullman et al. and Goldfine et al. be reconsidered and withdrawn.

Claim 2 has been rejected under §103(a) as being unpatentable over Coassin et al. in view of Ullman et al. and Goldfine et al. as applied to claims 1, 3, and 4 above, and further in view of U.S. Patent No. 4,517,289 to Milford et al. Claim 2 further limits claim 1 by reciting that the labeled antibodies are in dried form.

As discussed above, Coassin et al., Ullman et al. and Goldfine et al. have been distinguished from the claimed invention. The Examiner admits that Coassin et al. do not teach the labeled monoclonal antibodies in dried form. The Examiner has cited Milford et al. because Milford et al. disclose the use of antibodies in stable form (e.g. lyophilized, frozen or in solution).

Milford et al. relates to the preparation of a hybridoma cell-line and the use thereof in the production of antibodies suitable to identify human tissue. Applicants respectfully submit that the Examiner has not established the motivation or suggestion in the prior art to combine the teachings of Milford et al. with the teachings of Coassin et al., Ullman et al and Goldfine et al. In addition, upon combining the above references, one of ordinary skill in the art would not arrive at the claimed test system or anything remotely close to it. There is no suggestion in the cited art to address the need for a real time test system to assay insulin.

In order to establish a *prima facie* case of obviousness, one of the criteria to be met is that the prior art references, when combined, must teach or suggest all of the claim limitations. See MPEP §2142.

The important aspects of the claimed invention have been discussed above. Upon combining the teachings Milford et al. with Coassin et al., Ullman et al. and Goldfine et al., all of Applicants' claimed limitations are not taught or suggested. Therefore, based on the foregoing discussion, Applicants' claimed invention is not obvious over Milford et al. in view of Coassin et al., Ullman et al. and Goldfine et al.

Accordingly, Applicants respectfully request that the rejection under §103 (a) based on Milford et al. in view of Coassin et al., Ullman et al. and Goldfine et al. be reconsidered and withdrawn.

Claims 15-18 have been rejected under §103(a) as being unpatentable over Coassin et al. in view of Ullman et al., Goldfine et al. and Milford et al. as applied to claims 1-4 above, and further in view of U.S. Patent No. 5,167,947 to Geary et al.

Claims 15-18 limit claims 1-4 by reciting that the sample of claims 1-4 is obtained by a probe arranged to be introduced into the *Vena splenica* and/or *Vena porta.* In the office action, the Examiner admits that Coassin et al. do not disclose obtaining a sample by a probe arranged to be introduced into the *Vena porta.*

The Examiner contends that because Geary et al. disclose obtaining a sample by insertion of a catheter in the portal vein, it would have been obvious to one of ordinary skill in the art to obtain a sample as taught by Geary et al. for the device of Coassin et al. Applicants disagree.

Geary et al. disclose pharmaceutical compositions, such as ethylene diamino tetracetic acid, for the enhancement of absorption of certain drugs in the gastrointestinal tract. There is no suggestion to utilize the teachings of Geary et al. in a real time test system, such as that of the claimed invention.

Again, Applicants respectfully submit that the Examiner has not established the motivation or suggestion in the prior art to combine the teachings of Geary et al. , Milford et

al., Coassin et al., Ullman et al and Goldfine et al. In addition, upon combining the above references, one of ordinary skill in the art would not arrive at the claimed test system. Moreover, there is no suggestion in the cited art to address the need for a real time test system to assay insulin.

In order to establish a *prima facie* case of obviousness, one of the criteria to be met is that the prior art references, when combined, must teach or suggest all of the claim limitations. See MPEP §2142.

The important aspects of the claimed invention have been discussed above. Upon combining the teachings Geary et al. with Milford et al., Coassin et al., Ullman et al. and Goldfine et al., all of Applicants' claimed limitations are not taught or suggested. Therefore, based on the foregoing discussion, Applicants' claimed invention is not obvious over Geary et al., in view of Milford et al., Coassin et al., Ullman et al. and Goldfine et al.

Accordingly, Applicants respectfully request that the rejection under §103 (a) based on Geary et al. in view of Milford et al., Coassin et al., Ullman et al. and Goldfine et al. be reconsidered and withdrawn.

In light of the foregoing amendments and remarks, Applicants respectfully submit that the application is now in condition for allowance. If the Examiner believes a telephone

discussion with the Applicant's representative would be of assistance, he is invited to contact the undersigned at his convenience.

Respectfully submitted,

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MARKED-UP VERSION SHOWING CHANGES

IN THE CLAIMS:

1. (Twice Amended) A real-time test system comprising at least one reservoir and at least one photomultiplier detector;

wherein said reservoir ~~comprising~~ comprises monoclonal anti-insulin or anti-C peptide capture antibodies solidified in said reservoir, and

wherein said reservoir is capable of receiving a sample, a wash solution, and labeled monoclonal anti-insulin or anti-C peptide antibodies useful as a tracer; and

wherein said labeled antibodies allow photometrical detection.